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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/063,599	05/03/2002	Dan L. Eaton	10466/365	4659

9157 7590 02/21/2006

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EXAMINER	
WEGERT, SANDRA L	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 02/21/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/063,599	EATON ET AL.	
	Examiner	Art Unit	
	Sandra Wegert	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 November 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 May 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/23/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The Information Disclosure Statement, sent 23 November 2005, has been entered. Claims 1-5 are pending in the instant application. Claim 1 has been amended. Claim 6 has been cancelled (27 September 2004).

Withdrawn Objections and Rejections

Any objection or rejection of record which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

Claim Rejections - 35 USC §§ 101 and 112

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

Claims 1-5 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility, one skilled in the art clearly would not know how to use the claimed invention.

The basis for these rejections is set forth in the previous Office Action mailed 23 August 2005 at pages 2-6.

Applicant's arguments (pp. 3-22 of the amendment received 23 November 2005) have been fully considered but are not found to be persuasive for the following reasons. Applicant reviews the legal standard for patentable utility, with which the examiner takes no issue.

Applicant argues that Example 30 of the present application provides sufficient disclosure to establish a specific, substantial and credible utility for the nucleic acids encoding the PRO polypeptide, that is, Example 30 discloses that PRO1327 is significantly overexpressed in normal human tissues (esophagus, stomach and lung) as compared to cancerous human tissue. Applicant submits that these data demonstrate that PRO1327 of the present invention is useful as diagnostic markers for the presence of one or more normal tissues in which it is significantly overexpressed.

Applicant argues that the Haynes et al. and Gygi et al. publications do not support the rejection (Remarks, page 15, 23 November 2005). Applicant characterizes Haynes et al. and Gygi et al. as teaching that there is a general trend of increased protein levels from increased mRNA levels, and that there is a positive correlation between mRNA and protein amongst most of the 80 or 150 yeast proteins studied but the correlation is "not linear" and hence, one cannot accurately predict protein levels from mRNA levels. Applicants submit that the Haynes data meets the "more likely than not standard" and shows that a positive correlation exists between mRNA and protein.

It is not disputed that Haynes et al. and Gygi et al. shows that there is a slight general

trend that increased transcript levels may correlate with increased protein levels, but there are many publications that demonstrate no correlation, which will be discussed below.

One paper showing poor correlation is Anderson et al., Electrophoresis, Vol. 18, pages 533-537, 1997, (submitted by Applicant, 23 November 2005) who found that there was a poor correlation (0.48) between mRNA and protein levels in liver cells (abstract, page 535). They suggest that the two major phases of gene expression regulation (transcription through message degradation on the one hand, and translation through protein degradation on the other) are of approximately equal importance in determining the net output of proteins (page 536, left column). Anderson et al. also reanalyzed the set of data for plasma proteins secreted by the liver that was published by Kawamoto et al., (Gene, 1996, Vol. 16, pages 1977-1981), in which the mRNA-to-protein relationship for nine plasma proteins was 0.96. However, when albumin (which is well-separated from the cluster of the remaining eight and thus exercises a disproportionate influence on the correlation coefficient) was omitted from the calculation, the correlation coefficient is reduced to –0.19, which suggests a very poor correlation (page 536, right column). Lian et al., (2001, Blood 98:513-524) show a lack of correlation between mRNA expression and protein expression in mouse cells (see p. 514, top of left column: "The results suggest a poor correlation between mRNA expression and protein abundance, indicating that it may be difficult to extrapolate directly from individual mRNA changes to corresponding ones in protein levels."). See also Fessler et al., (2002, J. Biol. Chem. 277:31291-31302) who found a "[p]oor concordance between mRNA transcript and protein expression changes in human cells" (p. 31291, abstract). The evidence as a whole clearly indicates that one skilled in the art would not assume that an increase in mRNA levels results in increased protein levels without doing the

empirical experimentation necessary to measure protein levels. The requirement for such empirical experimentation indicates that the asserted utility for the claimed polypeptides is not substantial; it is not in currently available form.

Applicant's discuss the declaration previously submitted by Dr. Grimaldi, stating: "[o]ffice personnel must accept an opinion from a qualified expert" (underlined in original) (Remarks, page 10). In assessing the weight to be given expert testimony, the examiner may properly consider, among other things, 1) the nature of the fact sought to be established, 2) the strength of any opposing evidence, 3) the interest of the expert in the outcome of the case, and 4) the presence or absence of factual support for the expert's opinion. See Ex parte Simpson, 61 USPQ2d 1009 (BPAI 2001), Cf. Redac Int'l. Ltd. v. Lotus Development Corp., 81 F.3d 1576, 38 USPQ2d 1665 (Fed. Cir. 1996), Paragon Podiatry Lab., Inc. v. KLM Lab., Inc., 948 F.2d 1182, 25 USPQ2d 1561, (Fed. Cir. 1993). 1) In the instant case, the nature of the facts sought to be established is whether or not the unmeasured "two-fold" difference in DNA levels between normal tissues and cancerous tissues provides meaningful results. The declaration of Dr. Grimaldi does not teach the level of reproducibility or the level of reliability of the results. There are no relative or absolute levels of PRO1327 cDNA in control or tumor tissue disclosed. Neither the specification nor the declaration provide any evidence that indicates what the differences were or if they were statistically significant. If a clinician took a lung tissue sample from a patient with lung cancer, for example, what is the likelihood that when compared with normal tissue, the level of PRO1327 from the patient would be higher? How many samples would be needed? What sensitivity would be needed? Would the normal tissue have to be a pooled sample or could it be from a single individual? Would a universal normal control be

necessary or would a normal tissue matched sample be a sufficient control for comparison? Applicants have provided no indication of the nature or number of samples that were used. The only thing Applicants teach is that PRO1327 cDNA was "overexpressed", and this does not enable the skilled artisan to differentiate between expression levels in order to diagnose any diseases. 2) Regarding the strength of opposing evidence, the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue (for example, see Hu et al. 2003, Journal of Proteome Research 2:405-412, of record). Without more specifics about necessary sample size, expression level range for normal and tumor tissues, the specification has not provided the invention in a form readily usable by the skilled artisan such that significant further experimentation is unnecessary. 3) Regarding the interest of the expert in the outcome of the case, it is noted that Dr. Grimaldi is employed by the assignee and is an inventor in this application. 4) Finally, with regard to the presence or absence of factual support for the expert's opinion, it is noted that while the declaration Dr. Grimaldi discusses findings in terms of "a majority of cases", no data, percentage increases or levels of significance are disclosed, making it difficult for the Examiner independently to draw conclusions.

Applicants submit that the statistical analysis by Hu et al. is not a reliable standard (Remarks, p. 17) because the frequency of citation only reflects the current research of interest of a molecule but not the true biological function of the molecule. Applicant criticizes Hu et al. as being based on a statistical analysis of information published in the literature. This has been fully considered but is not found to be persuasive. The asserted utility for the claimed polypeptide is based on the presumption that increased cDNA production leads to increased mRNA and

increased protein production. Hu et al. is directly on point by showing that the presumption is incorrect when designating proteins as diagnostic markers for cancer. Hu et al. (2003, Journal of Proteome Research 2:405-412) analyzed 2286 genes that showed a greater than l-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column) and discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a l0-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section). The instant specification does not disclose that PRO1327 cDNA levels are expressed at l0-fold or higher levels compared with normal, matched tissue samples. Therefore, based on Hu et al., the skilled artisan would not reasonably expect that PRO1327 polypeptide can be used as a cancer diagnostic. Since the asserted utility for the claimed polypeptides is not in currently available form, the asserted utility is not substantial.

Applicant criticizes Hu et al. as using faulty statistical analysis. This has been fully considered but is not found to be persuasive. Applicant is holding Hu et al. to a higher standard than their own specification, which does not provide proper statistical analysis such as reproducibility, standard error rates, etc.

Applicant discusses the Utility Guidelines, in which Office personnel are cautioned to be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the substantial, or "real world" utility

prong of the utility requirement. Applicant submits that the present application clearly demonstrates that the nucleic acid of SEQ ID NO: 91 that encodes PRO1327 is significantly differentially expressed in normal tissues, and therefore the nucleic acid, protein and claimed antibodies meet the utility requirement of 35 USC 101 as a diagnostic marker for normal tissues.

Applicants' arguments have been fully considered but are not deemed persuasive. Since the asserted utility for the polynucleotides and polypeptides is not in currently available form, for the reasons discussed above, the asserted utility is not substantial. Based on consideration of the totality of the evidence, it is proper to maintain the rejections.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eileen B. O'Hara, whose telephone number is (571) 272-0878. The examiner can normally be reached on Monday through Friday from 10:00 AM to 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached at (571) 272-0961.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://portal.uspto.gov/external/portal/pair. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Eileen B. O'Hara

SLW
14 February 2006

EILEEN B. O'HARA
PATENT EXAMINER